**Human BATF+ IL-4+ T follicular helper cells are linked to a polarized IgG4 switching event and accumulate primarily outside germinal centers in IgG4-related disease lesions**

Takashi Maehara\(^a\) Hamid Mattoo\(^b\) John H. Stone\(^b\) and Shiv Pillai\(^a\)

\(^a\)Ragon Institute of MGH, MIT and Harvard, Massachusetts General Hospital, Harvard Medical School, Boston, MA
\(^b\)Division of Rheumatology, Allergy, & Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

**Objective:**

Although the germinal center is considered to be a major site of isotype switching, it is unclear whether class switching occurs primarily at the T-B interface outside germinal centers or within the light zone of the germinal center. We show here that IL-4 expressing T follicular helper (T\(_{FH}\)) cells are sparse in human secondary lymphoid organs and are primarily located outside germinal centers. In IgG4-related disease (IgG4-RD), a disorder characterized by polarized Ig class switching and prominent tertiary lymphoid organs, most T\(_{FH}\) cells in disease lesions make IL-4.

**Methods:**

We used quantitative multicolor immuno-fluorescence to identify IL-4 secreting T\(_{FH}\) cells in secondary lymphoid organs from healthy individuals and affected tissues from IgG4-RD and Sjögren's syndrome (SS) with active disease.

**Results:**

The relative proportion of IL-4 expressing T\(_{FH}\) cells is 10-20 fold higher in disease lesions compared to control secondary lymphoid organs. These IL-4 expressing T\(_{FH}\) cells are found in tertiary lymphoid organs but are primarily located outside germinal centers and large numbers of IgG4 expressing B cells are also seen in their vicinity. Human IL-4\(^+\) T\(_{FH}\) cells do not express GATA-3 but express BATF. In contrast to the situation in IgG4-RD, IL-4\(^+\) T\(_{FH}\) cells are rarely found in or around germinal centers in SS, a disorder in which IgG4 is not elevated. The proportion of CD4\(^+\) IL-4\(^+\) BATF\(^+\) T cells as well as of CD4\(^+\) IL-4\(^+\) CXCR5\(^+\) T cells in IgG4-RD tissues correlates tightly with tissue IgG4 plasma cell numbers and plasma IgG4 levels in patients but not with the total plasma levels of other isotypes.

**Conclusions:**

These data describe a T\(_{FH}\) sub-population in human tertiary lymphoid organs with IgG4-RD that is linked to a very specific Ig isotype switching event in vivo and support the view that isotype switching occurs primarily outside germinal centers.